

Lean NAFLD: A Not So Benign Condition?

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Nonalcoholic fatty liver disease (NAFLD) is a worldwide epidemic with global prevalence estimated at 25%.⁽¹⁾ Although NAFLD is usually associated with obesity, patients who are not obese can also present with NAFLD; this is known as “lean NAFLD.” Lean NAFLD is defined as NAFLD that develops in patients with a body mass index (BMI) $<25 \text{ kg/m}^2$. The prevalence of lean NAFLD varies from 7% in the United States⁽²⁾ to as high as

19% in Asia.^(3,4) Unfortunately, being lean (not overweight) does not necessarily lead to better health. A recent large meta-analysis by Sookoian and Pirola⁽⁵⁾ of almost 2,000 patients with NAFLD who were lean demonstrated that patients with NAFLD who are lean or obese share a common altered metabolic and cardiovascular profile, which in turn may lead to collective risk for adverse cardiometabolic outcomes, including diabetes and ischemic heart disease. Indeed, atherosclerotic cardiovascular disease remains the most common cause of death in all weight categories. The increase in cardiometabolic risk in lean NAFLD has been attributed primarily to alterations in body fat distribution, in particular visceral adiposity as measured by waist circumference or waist-to-hip ratio.⁽⁵⁻⁷⁾ In fact, measures of abdominal adiposity may best predict development of severe liver disease in NAFLD.⁽⁶⁾ Severity of NAFLD is also driven, in part, by single-nucleotide polymorphisms in genes involved in lipid metabolism, oxidative stress, insulin signaling, and fibrogenesis.⁽⁸⁾ Genetic polymorphisms in the patatin-like phospholipase domain-containing-3 (*PNPLA3*) gene, which is related to lipid transformation, is now recognized as the major common genetic determinant of NAFLD and is associated with progression to non-alcoholic steatohepatitis (NASH) in both lean and obese NAFLD.^(7,8) In addition, alterations in the transmembrane 6 superfamily member 2 (*TM6SF2*) gene, which confers a susceptibility to NASH and fibrosis but protection against cardiovascular events, has been shown to be increased in lean NAFLD compared to patients with NAFLD who are overweight/obese.⁽⁷⁾ However, studies to date in lean NAFLD have been severely limited by small sample size and lack of natural history data with histologic assessment of NAFLD at baseline.

In the current issue, Hagström et al.⁽⁹⁾ report retrospective findings from the largest and longest series of patients with biopsy-proven NAFLD to date ($n = 646$), with a mean follow-up time of 19.3 years. The lean NAFLD prevalence in this cohort was high at 19% ($n = 123$; Fig. 1). The cohort was derived from three large Swedish university hospitals and comprised all patients with biopsy-proven NAFLD from 1971

Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Lisa B. VanWagner, M.D., M.Sc.
Northwestern University, Feinberg School of Medicine
Departments of Medicine-Division of Gastroenterology and
Hepatology and Preventive Medicine
676 N. St. Clair Street, Suite 1400
Chicago, IL 60611
E-mail: lvw@northwestern.edu
Tel: +1-312-695-1632

or

Matthew Armstrong, M.R.C.P., Ph.D.
University of Birmingham
Centre for Liver Research and NIHR Biomedical
Research Unit
Edgbaston, Birmingham B15 2TT
United Kingdom
E-mail: armstrong@bham.ac.uk
Tel: +44-796-8470622

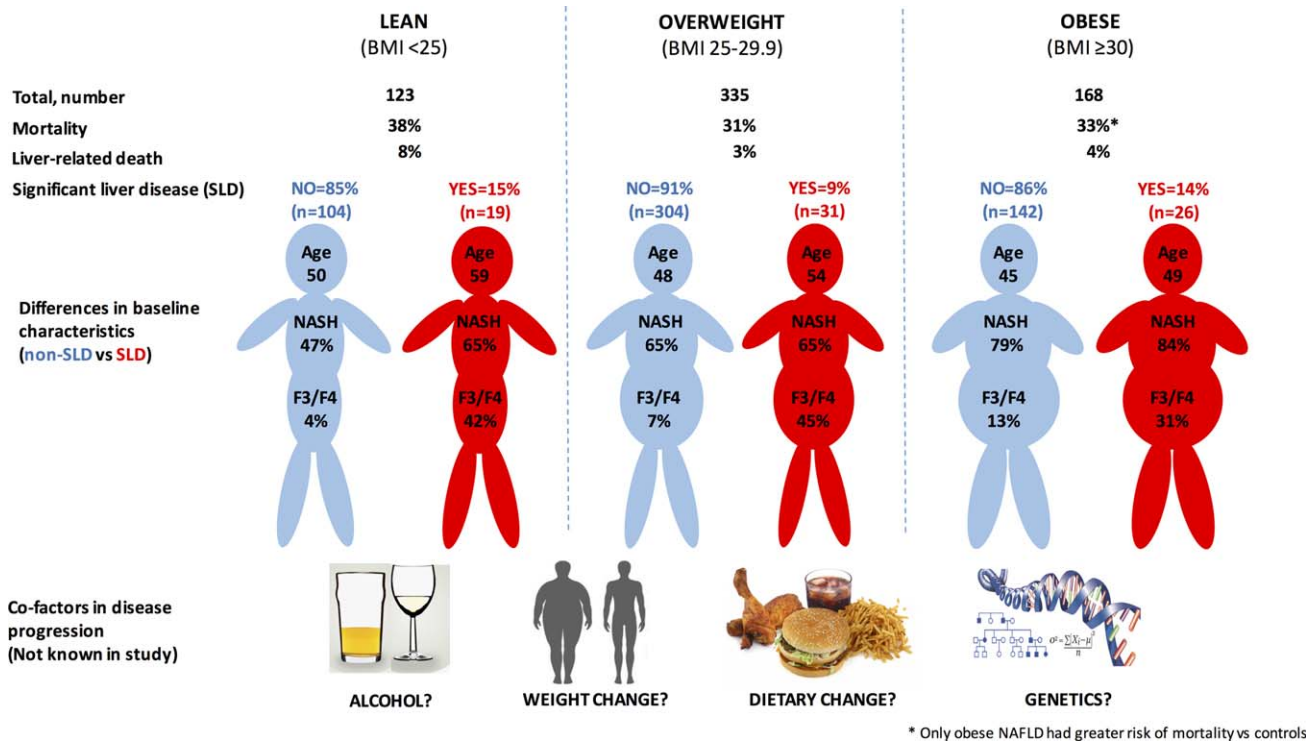


FIG. 1. Schematic summary of the study by Hagström et al. Abbreviation: SLD, significant liver disease.

through 2009. Importantly, liver pathology was centrally re-reviewed by a single pathologist, and outcomes were ascertained through data linkage with the Swedish national registries, a major strength of the study. In order to assess the impact of NAFLD across weight categories on mortality, subjects were matched to a control population by age, sex, and municipality.

The authors report several interesting findings that warrant further exploration. First, compared to age and sex-matched controls, there was no increased mortality in lean (or overweight) NAFLD; mortality in NAFLD was increased only in those patients with obesity (BMI >30 kg/m²). These findings are consistent with several other studies demonstrating that mortality risk is restricted to those with obesity in NAFLD.⁽¹⁰⁾ Only one study, published in abstract form only, has reported an increased risk of death in lean NAFLD. In 2014, Dela Cruz et al.⁽¹¹⁾ observed 1,090 patients with biopsy-proven NAFLD; this study was a comparison of 125 lean NAFLD and 965 nonlean (BMI ≥ 25) individuals enrolled from multiple centers across several continents. Overall mortality was calculated in a subset of patients (n = 483) who underwent biopsy prior to 2005. With a mean of 11.1 years of follow-up

in this subset, 71 patients died (14.7%). Cumulative survival was shorter in lean NAFLD compared to those with nonlean NAFLD.

Second, despite lower prevalence of advanced fibrosis and a more favorable metabolic risk profile at baseline, patients with lean NAFLD were more likely than patients with NAFLD who were overweight to develop severe liver disease (19/123 versus 31/335; Fig. 1). Importantly, although the metabolic profile was more favorable, patients with lean NAFLD could still not be classified as “healthy,” with nearly one third having coexistent hypertension and a mean total cholesterol of 232 mg/dL (6 mmol/L) at baseline. Unfortunately, intricate measures of central adiposity (i.e., waist circumference, bioimpedance) and organ-specific insulin resistance (in particular adipose tissue) were not available to provide a complete metabolic risk assessment at baseline. Remarkably, 50% of lean NAFLD had biopsy-proven NASH, which is much higher than what has been reported in general population studies.⁽¹⁾ This suggests selection bias toward a more severe lean NAFLD population, which is a criticism of most secondary/tertiary care observational studies and is mainly because liver biopsy was most likely performed

due to elevation in aminotransferases or presence of comorbidities, which in turn likely increases the pretest probability for NASH. A significant limitation of a retrospective analysis is the inability to fully assess indications for liver biopsy or include all persons with lean NAFLD by imaging into a biopsy cohort.

Finally, the authors identified three prognostic indicators for mortality in lean NAFLD: older age, fibrosis stage, and hypertension. These risk factors are not new and have been reported previously, in particular, advanced fibrosis.⁽¹²⁾ What is surprising is that of the 19 patients with lean NAFLD who developed severe liver disease, 58% (n = 11) had stage 0-2 fibrosis at baseline. As the authors discuss, this suggests accelerated development of advanced fibrosis in selected patients with lean NAFLD, albeit with over 20 years of follow-up and an entry age of 58 years. Although future studies are needed to confirm this finding and to elucidate potential pathophysiologic mechanisms underlying this observation, the bottom line is that carefully selected patients with lean NAFLD likely require long-term follow-up and reassessment of progression of liver disease over time. Even though numbers were small, it appears that those who developed severe liver disease in the lean NAFLD group (compared to the nondevelopers) were older (59 versus 50 years), had more severe portal inflammation (grade 2, 41% versus 7%), fibrosis stage 3 or 4 (42% versus 4%), and a higher prevalence of NASH (65% versus 47%) at baseline. In the absence of validation, these parameters could be cautiously used to guide which lean patients should be followed up in the future.

Several limitations temper the findings in this study and warrant mention. Because the data were assembled retrospectively, there is limited ability to determine whether or not subjects developed additional risk factors over time that are known to predispose to advanced liver disease. The authors address this somewhat by performing sensitivity analyses to assess the impact of incident diabetes on risk for severe liver disease. They found that diabetes development attenuates the association between lean NAFLD and development of severe liver disease but does not fully account for the observed association. Most importantly, prospective assessment of two key risk factors for liver disease progression, namely alcohol intake and weight changes, over time are not available in this cohort. Nineteen years is an extensive follow-up time. One might speculate that in the absence of identified advanced liver disease that patients with lean NAFLD may not have received counseling on alcohol minimization and thus consumed alcohol at at-risk levels for development of severe steatohepatitis. In addition, weight gain throughout adulthood as opposed to weight at a single

time point has been reported to be a risk factor for various lifestyle-related diseases, including NAFLD.⁽¹³⁾ In fact, a shift in body weight from normal weight to overweight or obesity is more strongly associated with the risk of NAFLD than maintenance of overweight/obesity.⁽¹³⁾ Thus, the change in adiposity over time is an important unmeasured confounder. In addition, previously hypothesized mechanisms related to genetic predisposition for severe liver disease (e.g., variants in *PNPLA3* or *TM6SF2*) and/or alterations in visceral adiposity were not collected in this study. Future studies addressing the potential mediators of the relationship between lean NAFLD and severe liver disease are needed.

Despite these limitations, the study by Hagström et al. provides important insights into our understanding of the natural history of lean NAFLD. Even though patients with NAFLD who are lean have no increased risk of mortality (hazard ratio, 1.04), the rates of progression to severe liver disease (most notably cirrhosis) highlight that lean NAFLD is not a simple benign condition. Further study of these “outliers” in the global NAFLD epidemic may provide important insights into the putative mechanisms linking hepatic steatosis to a myriad of clinical outcomes, including liver, cardiovascular, and cancer-related morbidity and mortality in NAFLD.

Lisa B. VanWagner ^{1,2}

Matthew J. Armstrong^{3,4}

¹Division of Gastroenterology and Hepatology,
Department of Medicine
Northwestern University Feinberg
School of Medicine
Chicago, IL

²Department of Preventive Medicine
Northwestern University Feinberg
School of Medicine
Chicago, IL

³Liver and Transplant Unit
Queen Elizabeth University Hospital Birmingham
Birmingham, United Kingdom

⁴National Institute for Health Research
Birmingham Biomedical Research Centre and
Centre for Liver Research
University of Birmingham
Birmingham, United Kingdom

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